Testosterone, the FDA and CVD Risk Controversies

Matt T. Rosenberg

Testosterone Deficiency

- Well established medical condition
- Confirmed by low serum concentrations of total T (e.g., < 200 ng/mL) drawn in early AM
- Negatively impacts
  - Male sexuality
  - General health
  - Quality of life

Symptoms of Testosterone Deficiency

- Decreased libido
- Erectile dysfunction
- Decreased energy
- Depressed mood
- Irritability
- Decreased sense of well being

Populations at High Risk of Testosterone Deficiency

- CHF
- Type 2 diabetes
- Obese
- COPD
- HIV
- Chronic opioid use

Various Comorbidities Associated with Hypogonadism

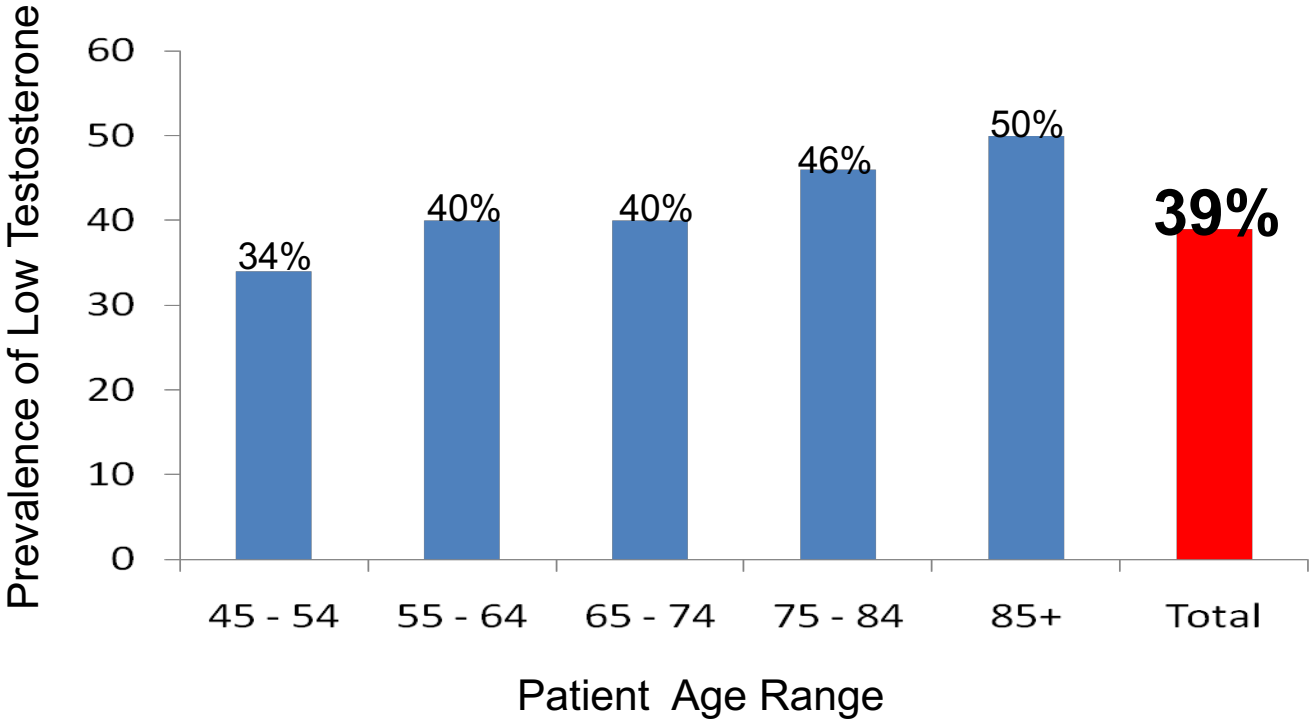
Condition	Odds Ratio
Obesity	2.38
Diabetes	2.09
Hypertension	1.84
Hyperlipidemia	1.47
Osteoporosis	1.41
Asthma/COPD	1.40

Mulligan T, Frick MF, Zuraw QC, et al. Int J Clin Pract. 2006;60(7):762-9.

Associated Chronic Medical Conditions

- Metabolic syndrome
- Diabetes
- Dyslipidemia
- Hypertension
- Renal failure frailty
- Malignancy
- Cardiovascular effects

The Prevalence of Low Testosterone Increases with Age (<300 ng/dL)



Adapted from
Mulligan T, Frick MF, Zuraw QC, et al. *Int J Clin Pract*. 2006;60(7):762-9.

Reality Check

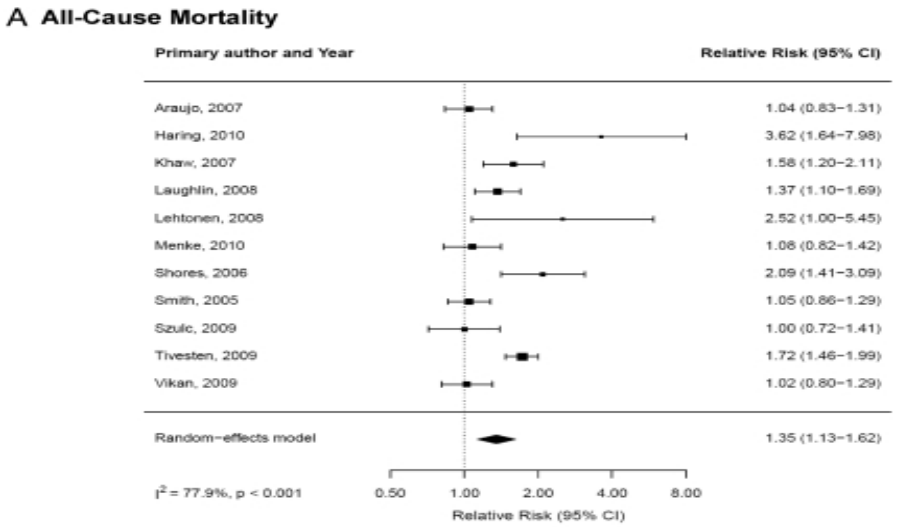
High testosterone levels is associated with decreased cardiovascular events

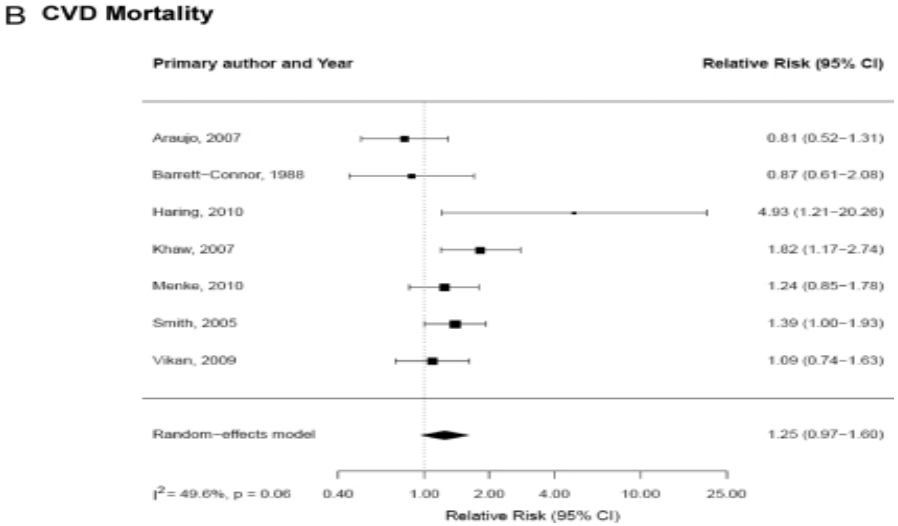
Low testosterone levels is associated with increased cardiovascular events

Higher testosterone associated with decreased risk of CV events

- 19 eligible articles looking at population based cohorts and case control studies
  - testosterone and atherosclerosis
  - stroke
  - myocardial infarction
  - ischemic heart disease
  - death from coronary heart disease or mortality
- Evidence in older population (>70), not younger

Ruige JB1, Mahmoud AM, De Bacquer D, Kaufman JM. Heart. 2011 Jun;97(11):870-5. doi: 10.1136/hrt.2010.210757. Epub 2010 Dec 21.





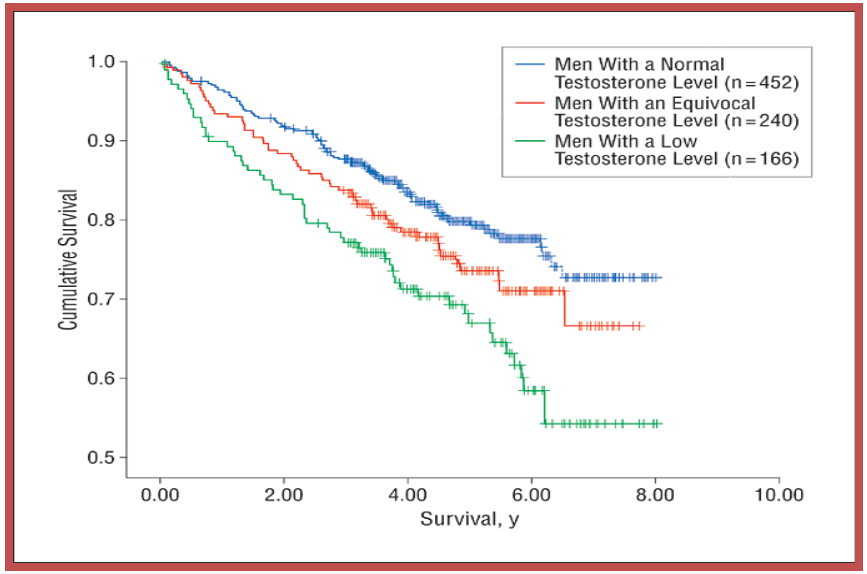
Meta-analysis of 18 studies and 22000 patients show lower T is significantly associated with overall and strongly associated with CV mortality

Araujo AB, Dixon JM, Suarez EA, Murad M, Guey LT, Wittert GA. J Clin Endocrinol Metab. 2011 Oct; 96(10): 3007–3019.

Low Testosterone and Increased Mortality

Studies	HR (95% CI)	Nature	Men, n	Follow-Up, yrs	Mortality
Shores, 2006	1.88 (1.34–2.63)	Retrospective	858	8	All-cause
Laughlin, 2008	1.38 (1.02–1.85)	Prospective	794	20	CVD
Khaw, 2007	2.29 (1.60–3.26)	Prospective	2314 of 11,606	10	All-cause/ CVD
Haring, 2010	2.32 (1.38–3.89)	Prospective	1954	7.2	All-cause
	2.56 (1.15-6.52)				CVD
Malkin, 2010	2.27 (1.45–3.60)	Prospective	930	6.9	All-cause in men with CAD
Tivesten, 2009	1.65 (1.29–2.12)	Prospective	3014	4.5	All-cause
Menke, 2010	1.43 (1.09–1.87)	Prospective	1114	9	All-cause
Vikan, 2009	1.24 (1.01–1.54)	Prospective	1568	11.2	All-cause
Pye 2014	2.3 (1.2-4.2) 3.0 if sex sx	Prospective	2599	4.3	All Cause/CVD
Jones 2013	2.02 (1.2-3.4)	Prospective	581	5.8	All cause
Corona, 2010	7.1 (1.8–28.6)	Prospective	1687	4.3	CVD
Muraleedharan et al, 2013	2.02 (1.2-3.4)	Prospective	581	5.8	All-cause
Hyde et al, 2012	1.62 (1.20- 2.19)	Prospective	4249	5.1	All-cause
	1.71 (1.12-2.62)				CVD
Lerchbaum et al, 2012	2.11 (1.60-2.79)	Prospective	2069	7.7	All-cause
	1.77 (1.23-2.55)				CVD

The Dilemma is that Low Testosterone Levels are Association with an Increased Mortality



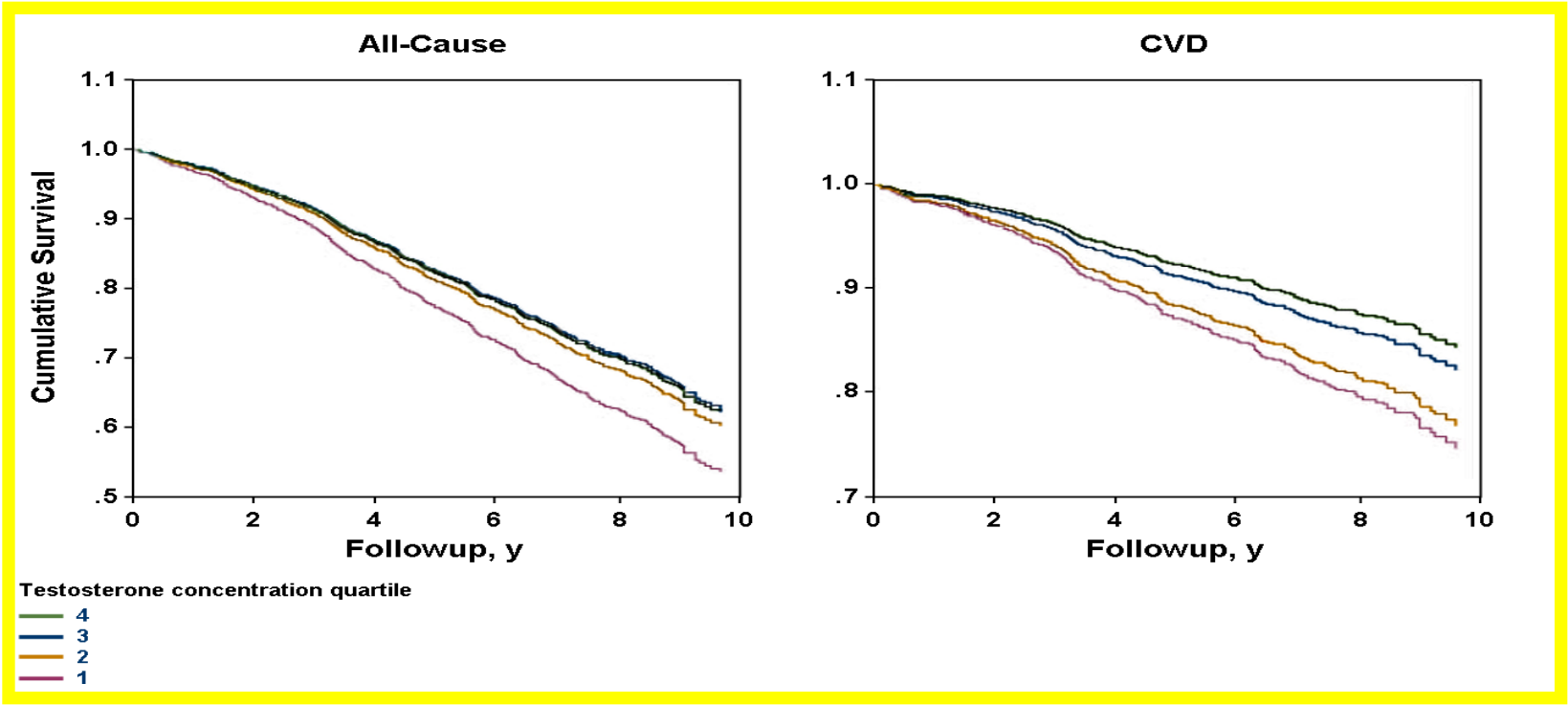
VA Puget Sound 8 year study of 858 men

Low T <250 ng/dL or a free T <0.75 ng/dL

All-cause mortality was 34.9% in men with low T and 20.1% in men with normal T

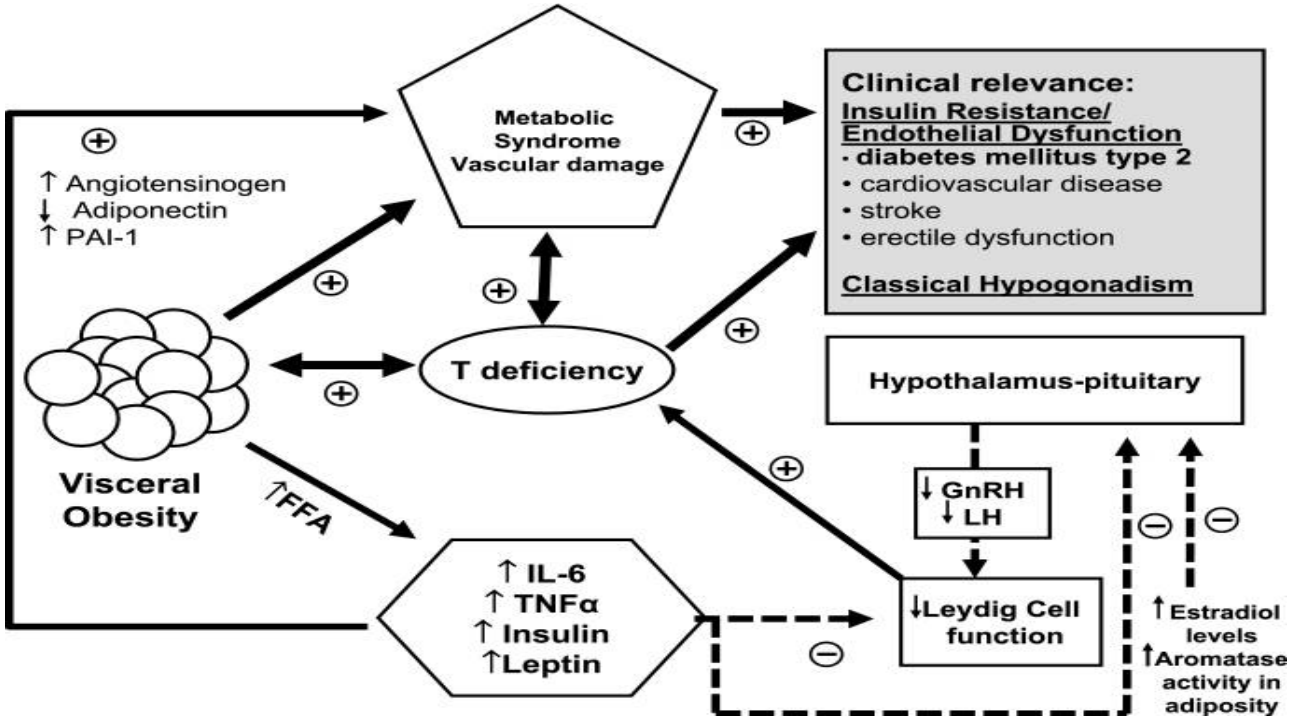
Shores MM, Matsumoto AM, Sloan KL, Kivlahan DR. *Arch Intern Med*. 2006;166(15):1660-1665.

Testosterone Levels are Related to All-Cause and CVD Mortality (EPIC)



Khaw KT, Dowsett M, Folkerd F, et al. *Circulation.* 2007;116(23):2694-2701.

What is the connection?



Why the controversy?


GOOD NEWS
BAD NEWS

The Bad News for Testosterone?

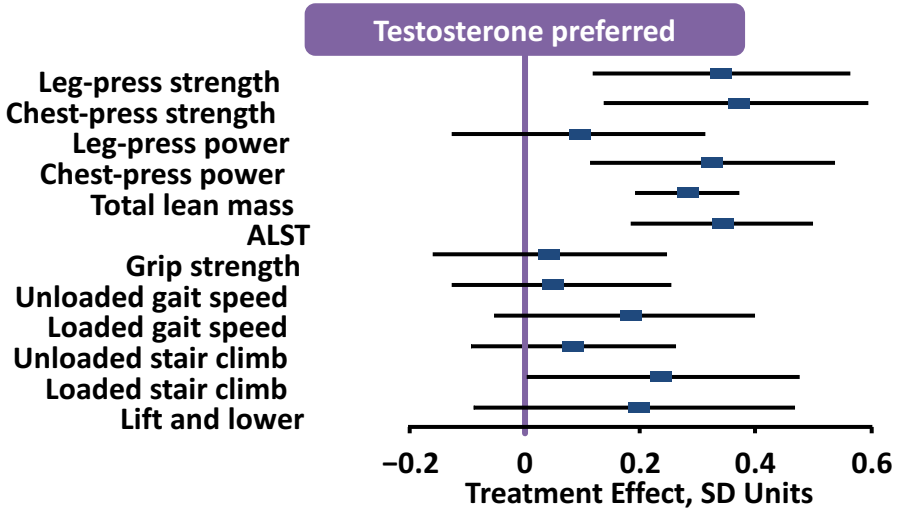
TOM Trial: Study Design

- Effect of testosterone therapy on lower-extremity strength and physical function in older, hypogonadal men with limitations in mobility
- Men aged ≥65 y (mean, 74 y) with serum TT 100-350 ng/dL or FT <50 pg/mL
- 209 participants randomized to receive testosterone gel or placebo for 6 months
- Testosterone gel titrated from 50 to 150 mg/d, based on serum testosterone level
- After dose adjustment, 16 men received 150 mg/d, 61 received 100 mg/d, and 29 received 50 mg/d
- Mean serum testosterone levels achieved were 574 (403) ng/dL in treatment group and 292 (160) ng/dL in placebo group
- Both groups had high prevalence of hypertension, obesity, diabetes, hyperlipidemia, and CVD

CVD = cardiovascular disease. FT = free testosterone.

Basaria S et al. *N Engl J Med.* 2010;363(2):109-122.

TOM Trial: Outcomes Show Benefit



Absolute treatment differences (testosterone vs placebo arms) are plotted for primary and secondary outcomes in units normalized to baseline standard deviation of measurement. Data are point estimates with 95% confidence intervals.

ALST = appendicular lean soft tissue. SD = standard deviation.

Adapted from: Travison TG, et al. *J Gerontol A Biol Sci Med Sci.* 2011;66(10):1090-1099.

TOM Trial: Safety

- In treatment arm, hematocrit and hemoglobin levels increased significantly, and HDL and LDL levels decreased
- TOM trial reported more cardiovascular AEs
  - 23 men receiving testosterone vs 5 receiving placebo
- Cardiovascular AEs had variable clinical importance
- Based on significantly increased incidence of cardiovascular AEs in treatment arm, data and safety monitoring board recommended cessation of enrollment and testosterone therapy:
  - Termination of study in December 2009

AE = adverse event.

Basaria S, et al. *N Engl J Med*. 2010;363(2):109-122.

TOM Trial: Shortcomings

- Originally not designed to assess adverse cardiovascular events, this study did not evaluate baseline cardiovascular function or preexisting conditions
- Did not account for the confounding effect of the possible sudden increase in physical activity due to supratherapeutic testosterone supplementation

Elkhoury FF, et al. Urology. 2017; (epub ahead of print).

Vigen, et al.
JAMA November 2013

Research

Original Investigation

Association of Testosterone Therapy With Mortality, Myocardial Infarction, and Stroke in Men With Low Testosterone Levels

Rebecca Vigen, MD, MSCS; Colin I. O'Donnell, MS; Anna E. Barón, PhD; Gary K. Grunwald, PhD; Thomas M. Maddox, MD, MSc; Steven M. Bradley, MD, MPH; Al Barqawi, MD; Glenn Woning, MD; Margaret E. Wierman, MD; Mary E. Plomondon, PhD; John S. Rumsfeld, MD, PhD; P. Michael Ho, MD, PhD

Association of TRT with Mortality, MI, and Stroke

Study Design	• Retrospective VA study of men with low testosterone levels (<300 ng/dL) who underwent coronary angiography
Population	• 1223 patients started testosterone after a median of 531 days following angiography • 7486 patients received no testosterone
Results	• 3 years after coronary arteriography, the Kaplan-Meier estimated cumulative percentages with events were **19.9% in the control group vs 25.7% in the TRT group** • Absolute risk difference of 5.8% at 3 years after coronary angiography • No difference in effect among those with and without coronary artery disease
Short-comings	• No randomization or placebo • 2 major corrections "Absolute risk" of MI (19.9 vs 25.7%) vs (21 vs 10%) • Exclusion of 1132 men • RETRACTION 29 societies

MI = myocardial infarction.

Vigen R, et al. *J Am Med Assoc*. 2013;310(17):1829-1836.

Vigen Trial: Shortcomings

- Testosterone dosage, duration of treatment and follow up levels not disclosed
- No randomization or placebo
- Using propensity score weighting to minimize residual confounding of the two groups

  Absolute risk of death, MI or stroke - -

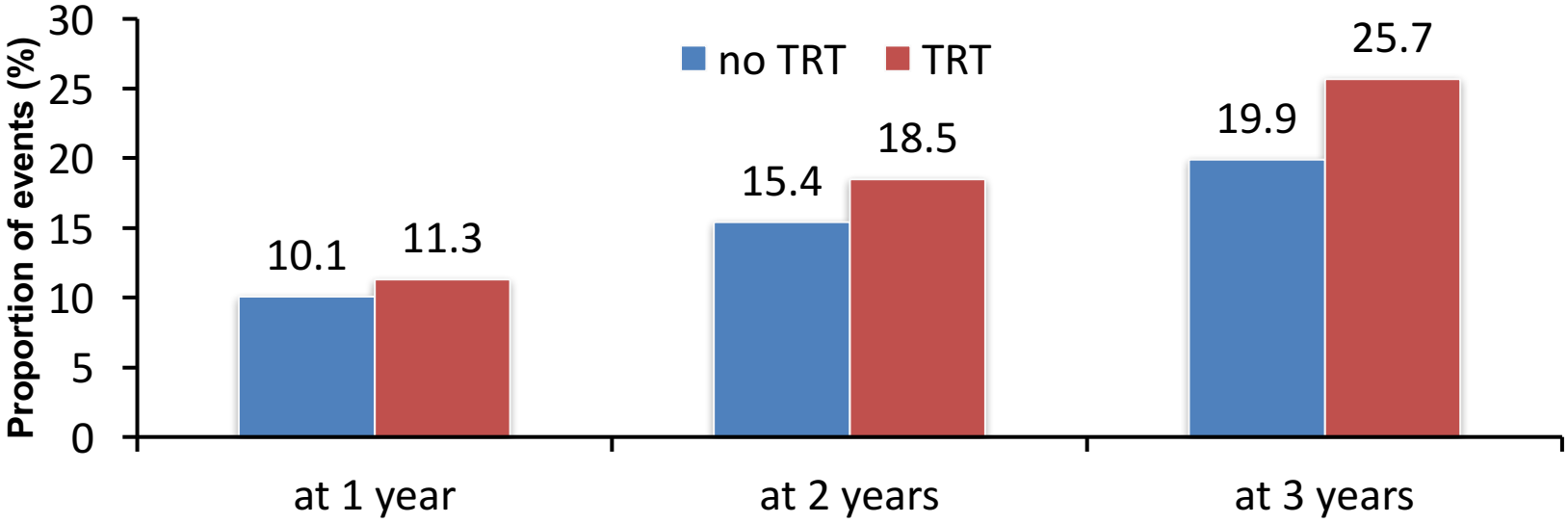
  19.9 placebo vs 25.7% treatment
- Raw data showed reverse effect

  Absolute risk of death, MI or stroke - -

  21.2% placebo vs 10% treatment
- Exclusion of 1132 men
- RETRACTION 29 societies

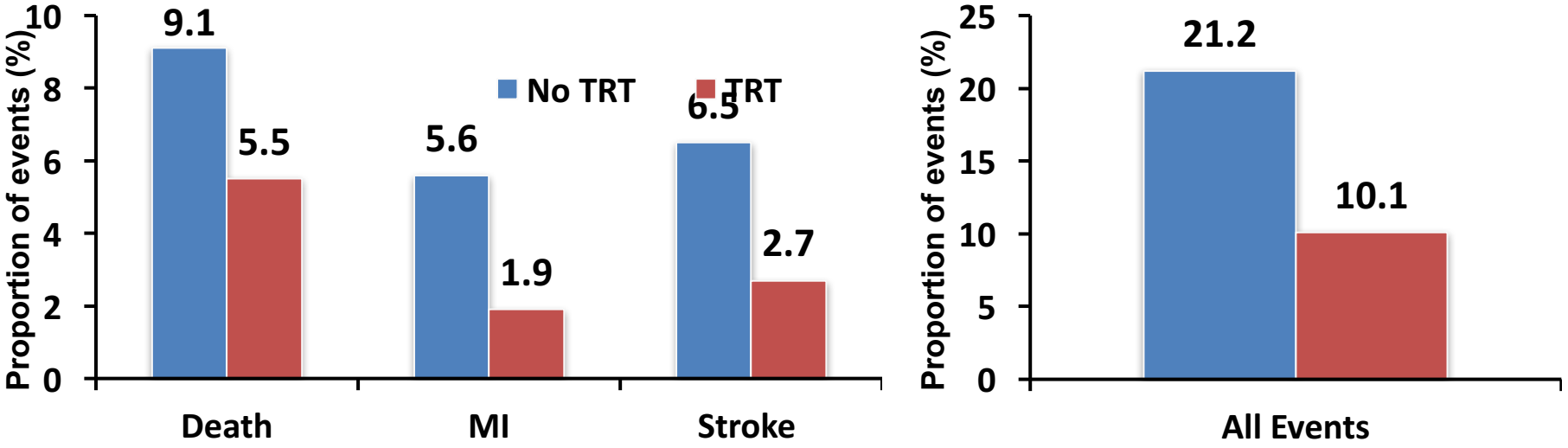
Elkhoury FF, et al. Urology. 2017; (epub ahead of print).

Proportion of All Events after Statistical Modeling: VIGEN Study



Vigen R, et al. *J Am Med Assoc*. 2013;310(17):1829-1836.

Proportion of All Events in Patients with Hypogonadism (%) with or Without TRT: VIGEN Study



Vigen R, et al. *J Am Med Assoc*. 2013;310(17):1829-1836.

Frinkle, et al.
PLOS One January 2014

OPEN ACCESS Freely available online

PLOS | ONE

Increased Risk of Non-Fatal Myocardial Infarction Following Testosterone Therapy Prescription in Men

William D. Finkle[1]*, Sander Greenland[2], Gregory K. Ridgeway[1], John L. Adams[1], Melissa A. Frasco[1], Michael B. Cook[3], Joseph F. Fraumeni Jr.[3], Robert N. Hoover[3]*

1 Consolidated Research, Inc., Los Angeles, California, United States of America, **2** Department of Epidemiology and Department of Statistics, University of California, Los Angeles, California, United States of America, **3** Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland, United States of America

Increased Risk of Non-fatal MI Following Testosterone Prescription

Study Design	• Retrospective cohort study of the risk of acute non-fatal MI in the 90 days following testosterone prescription
Population	• 55,593 patients started testosterone compared to 167,279 prescribed PDE5 inhibitors
Results	• In men <65 years, excess risk was confined to those with prior heart history, relative risk (RR) of 2.9 (1.49. 5.62) • In men >65 years, the 2-fold increased risk was associated with testosterone prescription regardless of CV history
Short-comings	• Retrospective study, no randomization, placebo or control • Serum testosterone before and after treatment are unknown • Testosterone dosages unknown • CV risk factors of subjects not discussed

PDE5 = phosphodiesterase type 5.

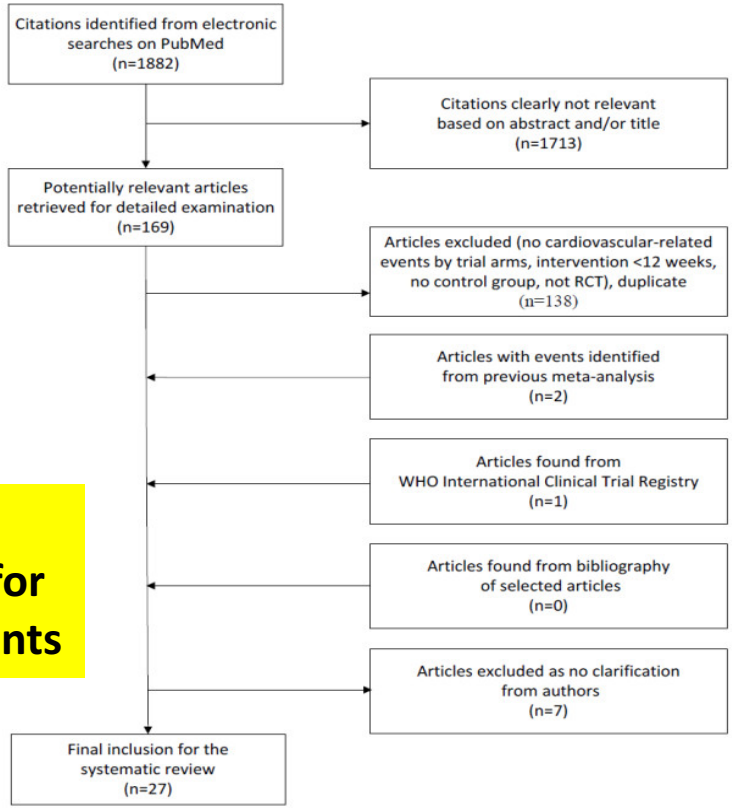
Frinkle WD, et al. *PLoS One*. 2014 Jan 29;9:e85805.
Elkhoury FF, et al. Urology. 2017; (epub ahead of print).

Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials

Study Design	• Meta-analysis of 27 placebo-controlled testosterone studies to assess CV events
Population	• Men receiving testosterone therapy 12+ weeks reporting cardiovascular-related events
Results	• Testosterone therapy increased risk of CV events (OR 1.54)
Short-comings	• Just 2 studies provided 1/3 of all CV events in T treat arm (one study was the TOM trial) • If exclude 2 studies CV events in T and placebo are identical

Xu L, et al. BMC Med. 2013; Published online 2013 Apr 18. doi: 10.1186/1741-7015-11-108
Elkhoury FF, et al. Urology. 2017; (epub ahead of print).

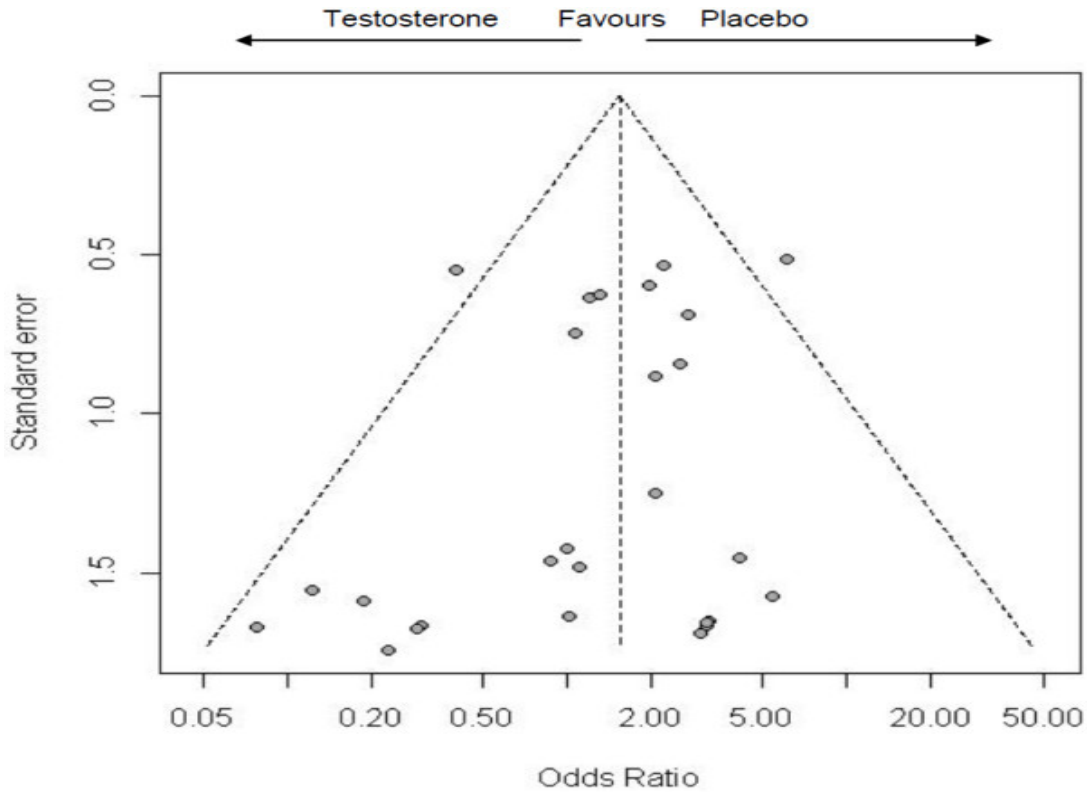
Xu Review: Shortcomings



2 of the 27 studies account for 35% of all CV events

Xu L, et al. BMC Med. 2013; Published online 2013 Apr 18. doi: 10.1186/1741-7015-11-108
Elkhoury FF, et al. Urology. 2017; (epub ahead of print).

Xu Review: Not All What it Seems



Xu L, et al. BMC Med. 2013; Published online 2013 Apr 18. doi: 10.1186/1741-7015-11-108

NY Times Editorial 2/5/14

- "substantial risks in prescribing testosterone to middle-age & older men for a variety of ailments." "testosterone **doubled the risk of CV** disease in more than 7,000 men who were 65 years +" "testosterone **tripled risk of heart attacks** in a group of more than 48,000 middle-age men with previous histories of heart disease."

- "the study provides the most compelling evidence yet that many American men have embarked on a perilous course of overtreatment "

- "testosterone is now being prescribed to men who are simply reluctant to accept the fact that they are getting older. "

FDA Advisory Board (Sep 17, 2014)

- Voted in favor for the FDA to impose stricter limitations on the T drug industry, particularly the language in product labels; this would clarify the appropriate therapeutic indications for TRT.
- With regards to the risk of CV events, the panelists confirmed that “evidence linking T therapy to an increased risk of heart attack, stroke & death is ‘inconclusive.”
- The panel further advised that the FDA should require drug manufacturers to conduct comprehensive studies to better assess the potential cardiovascular risks with TRT.

FDA Safety Announcement March 2015

FDA cautions about using testosterone products for low testosterone due to aging; requires labeling change to inform of possible increased risk of heart attack and stroke with use

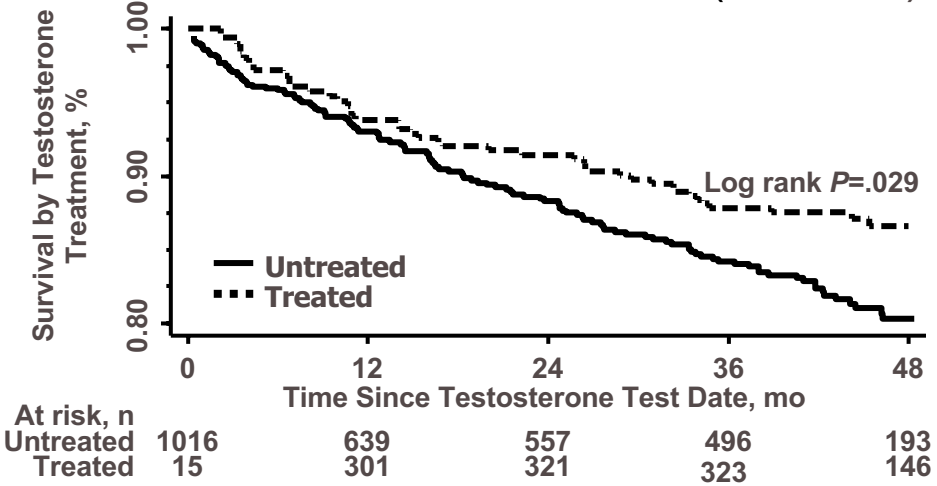
http://www.fda.gov/Drugs/DrugSafety/ucm436259.htm

The Good News for Testosterone?

Survival of Treated vs Untreated Testosterone-Deficient Men in VA Population: Does TRT Improve Mortality?

1031 men aged >40 years, T <250 ng/dL

Mortality: 10.3% treated, 20.7% untreated (*P*<.0001)



VA, US Department of Veterans Affairs.

Shores MM et al. *J Clin Endocrinol Metab.* 2012 ;97(6):2050-8.

Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality in men

Study Design	• A retrospective large observational cohort of 83010 male veterans with documented low total testosterone levels (TT) and no prior history or MI or stroke • The association of TRT with all-cause mortality, MI, stroke, and a composite endpoint was compared between these groups
Population	• 83 010 male veterans with documented low TT levels Group 1: TRT with normalization of TT(n=43931, median age 66, mean follow-up 6.2 years) Group 2: TRT without normalization of TT(n=25701, median age 66, mean follow-up 4.6 years) Group 3: Did not receive TRT(n=13378, median age 66, mean follow-up 4.7 years)
Results	• The all-cause mortality [hazard ratio (HR): 0.44, confidence interval (CI) 0.42–0.46], risk of MI (HR: 0.76, CI 0.63–0.93), and stroke (HR: 0.64, CI 0.43–0.96) were significantly lower in Gp1 vs. Gp3 in propensity-matched cohort. • All-cause mortality (HR: 0.53, CI 0.50–0.55), risk of MI (HR: 0.82, CI 0.71–0.95), and stroke (HR: 0.70, CI 0.51–0.96) were significantly lower in Gp1 vs. Gp2 . • There was no difference in MI or stroke risk between Gp2 and Gp3.
Conclusion	• Normalization of TT levels after TRT was associated with a significant reduction in all-cause mortality, MI, and stroke.

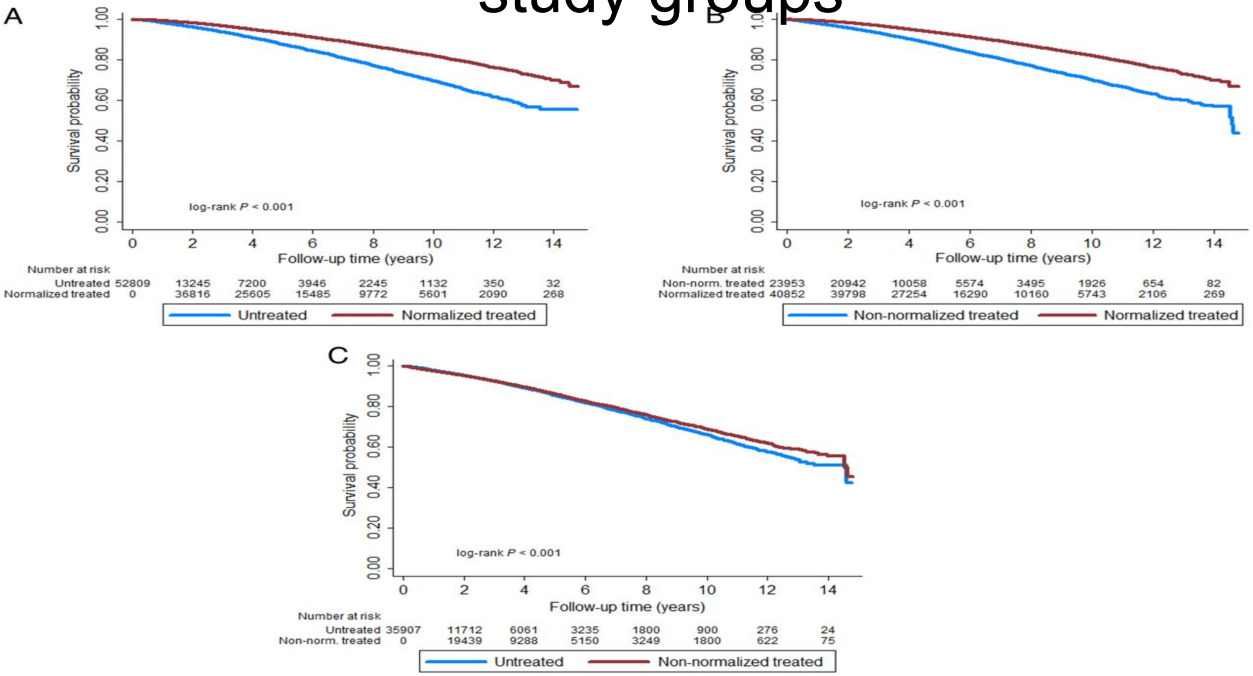
Sharma R, et al. Euro Heart J. 2015;36(40);2706-2715

Association of Testosterone Replacement With Cardiovascular Outcomes Among Men With Androgen Deficiency

Study Design	• A retrospective cohort study was conducted within an integrated health care delivery system • The primary outcome was a composite of cardiovascular end points that included acute myocardial infarction (AMI), coronary revascularization, unstable angina, stroke, transient ischemic attack (TIA), and sudden cardiac death (SCD)
Population	• Men at least 40 years old with evidence of androgen deficiency either by a coded diagnosis and/or a morning serum total testosterone level of less than 300 ng/dL • Men were to have received any TRT given by injection, orally, or topically
Results	• Median follow was 3.2 years (interquartile range [IQR], 1.7-6.6 years) in the never-TRT group (35,526 men) vs 4.2 (IQR, 2.1-7.8) years in the ever-TRT group (8808 men) • The rates of the composite cardiovascular end point were 23.9 vs 16.9 per 1000 person-years in the never-TRT and ever-TRT groups, respectively (HR, 0.67)
Conclusion	• Among men with androgen deficiency, dispensed testosterone prescriptions were associated with a lower risk of cardiovascular outcomes over a median follow-up of 3.4 years • Raw data was consistent with propensity scoring

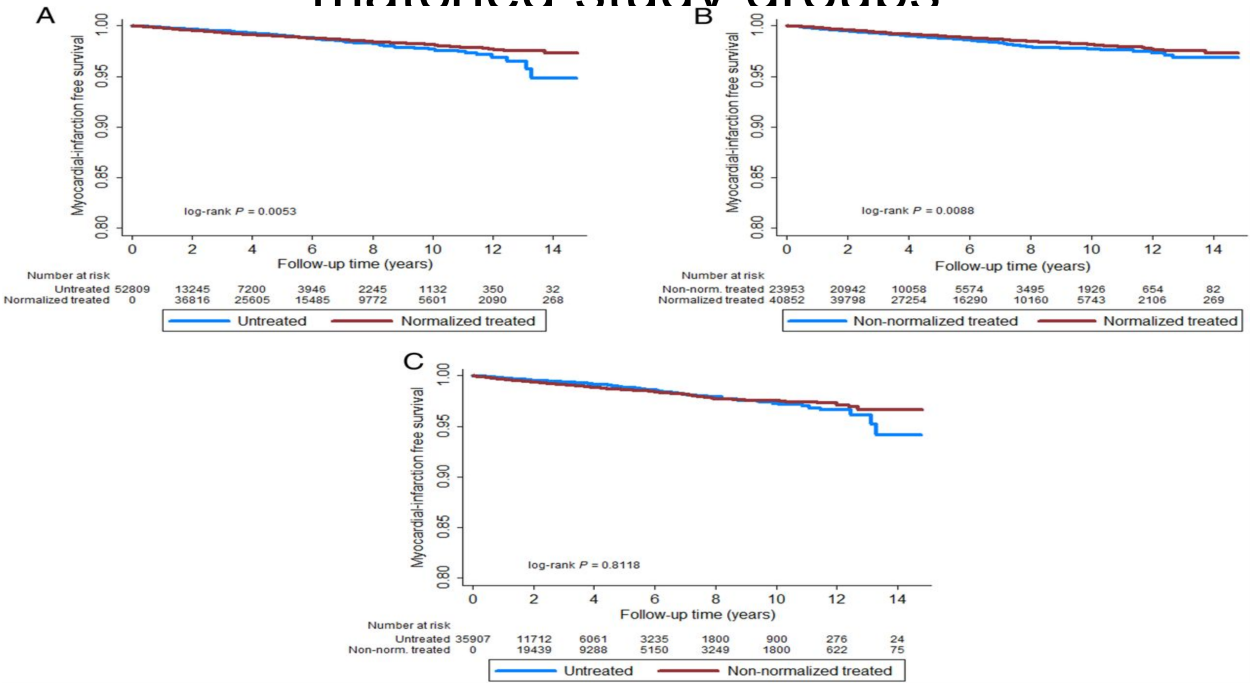
Cheetham TC, et al. Jama Intern Med. 2017;177(4):491-499

All-cause mortality among different propensity-matched study groups



From: Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality in men
Eur Heart J. 2015;36(40):2706-2715. doi:10.1093/eurheartj/ehv346

Myocardial infarction-free survival among different propensity-matched study groups



From: Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality in men
Eur Heart J. 2015;36(40):2706-2715. doi:10.1093/eurheartj/ehv346

Effects of Testosterone on Muscle Strength, Physical Function, Body Composition, and Quality of Life in Intermediate-Frail and Frail Elderly Men

Study Design	• Randomized, double-blind, placebo-controlled, parallel-group, single-center study • 6 months T treatment in intermediate-frail and frail elderly men, on muscle mass and strength, physical function, and quality of life
Population	• Community-dwelling elderly men at least 65-90 years of age with a total T at or below 12 nmol/liter or free T at or below 250 nmol/liter • 274 participants were randomized to transdermal T (50 mg/d) or placebo gel
Results	• Isometric knee extension peak torque improved in the T group (vs. placebo at 6 months), adjusted difference was 8.6 (95% confidence interval, 1.3-16.0; P = 0.02) Newton-meters • Lean body mass increased and fat mass decreased significantly in the T group by 1.08 +/- 1.8 and 0.9 +/- 1.6 kg, respectively. Physical function improved • Somatic and sexual symptom scores decreased with T treatment; adjusted difference was -1.2 (-2.4 to -0.04) and -1.3 (-2.5 to -0.2), respectively
Conclusion	• T treatment in intermediate-frail and frail elderly men with low to borderline-low T for 6 months may prevent age-associated loss of lower limb muscle strength and improve body composition, quality of life, and physical function.

Srinivas-Shankar U, et al. J Clin End Metab. 2010;95(2):639-50

Srinivas-Shankar: Frail Elderly Study

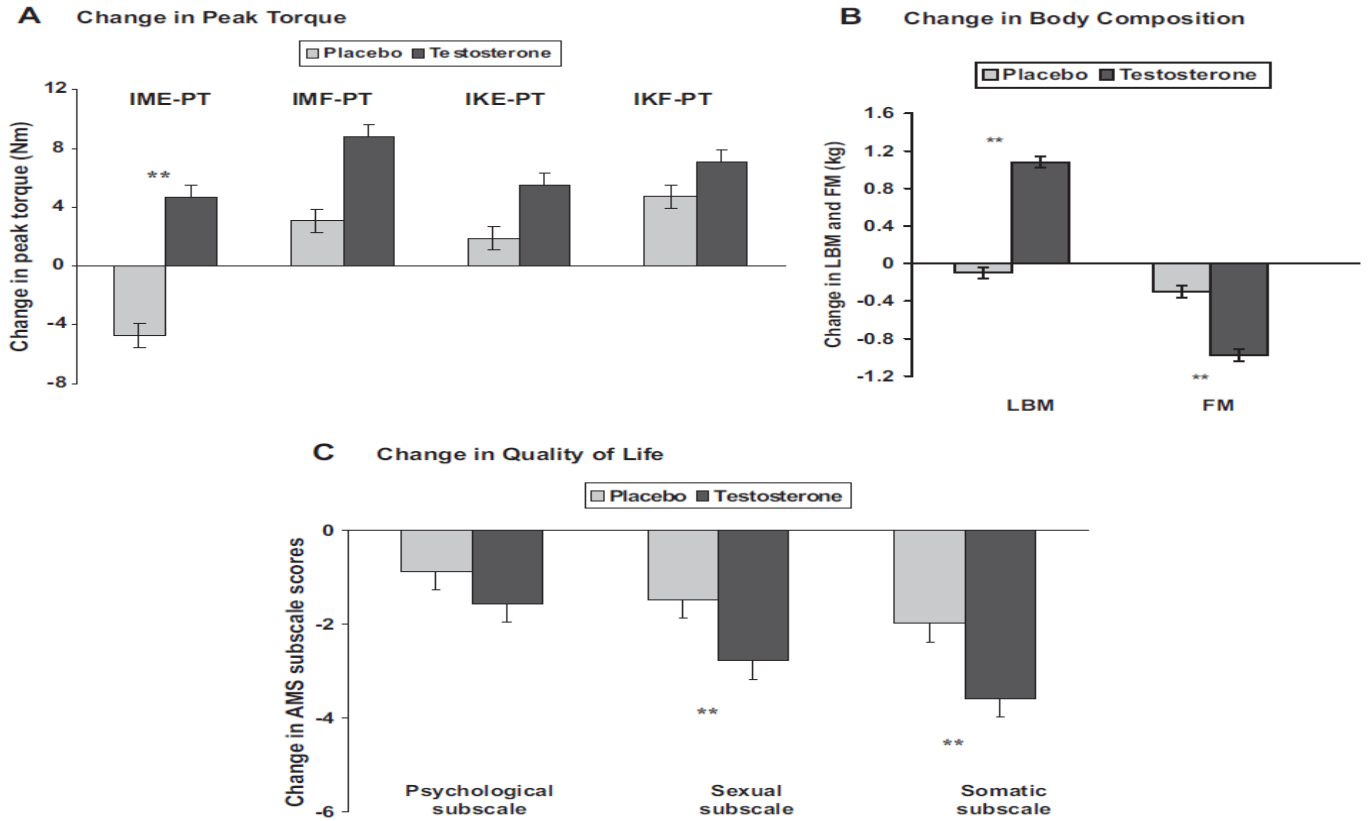


FIG. 3. A, Change in IME-, IMF-, IKE-, and IKF-PT in the placebo and T groups at 6 months; B, change in LBM and FM at 6 months compared with baseline in the placebo and T groups; C, change in AMS subscale scores at 6 months compared with baseline in the placebo and T groups. **, Significant difference between groups (ANCOVA, comparing adjusted mean difference between placebo and T groups).

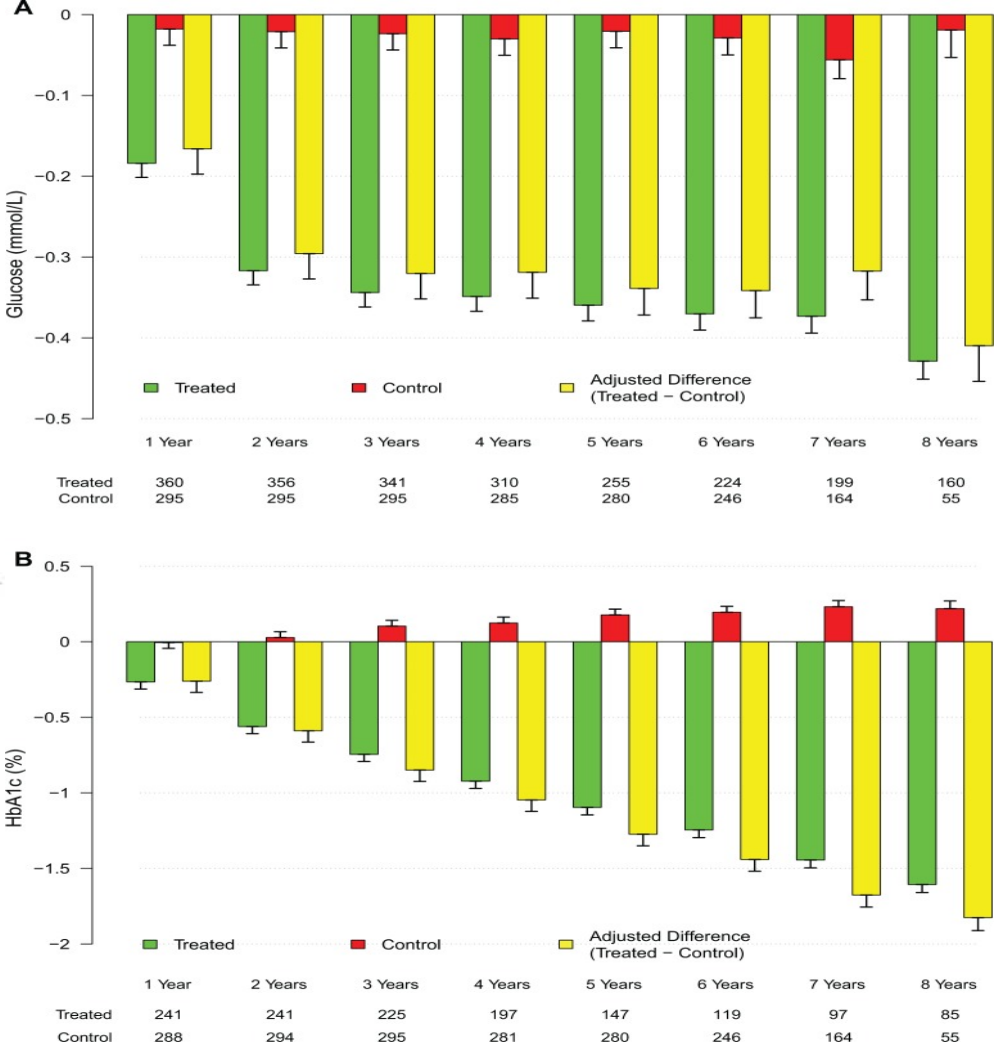
Srinivas-Shankar U, et al. J Clin End Metab. 2010;95(2):639-50

Long-Term Testosterone Therapy Improves Cardiometabolic Function and Reduces Risk of Cardiovascular Disease in Men with Hypogonadism: A Real-Life Observational Registry Study Setting Comparing Treated and Untreated (Control) Groups

Study Design	• Observational, prospective, cumulative registry study assess long-term effectiveness and safety of T in men in a urological setting.
Population	• 656 men (age: 60.7 ± 7.2 years) with total T levels ≤12.1 nmol/L and symptoms of hypogonadism • In the treatment group, men (n = 360) received parenteral T undecanoate (TU) 1000 mg/12 weeks following an initial 6-week interval for up to 10 years • Men (n = 296) who had opted against TTh served as controls • Median follow-up in both groups was 7 years
Results	• 2 deaths in the T-treated group, none was related to CV events • 21 deaths in the untreated (control) group, 19 of which were related to CV events • The estimated reduction in mortality for the T-group was between 66% and 92% • 30 nonfatal strokes and 26 nonfatal myocardial infarctions in the control group and none in the T-treated group
Conclusion	• Long-term TU was well tolerated with excellent adherence suggesting a high level of patient satisfaction • Mortality related to CV disease was significantly reduced in the T-group

Traish AM, et al. J Cardiovasc Pharmacol Ther. 2017;22(5):414-433

Long-Term Testosterone Therapy Improves Cardiometabolic Function and Reduces Risk of Cardiovascular Disease in Men with Hypogonadism



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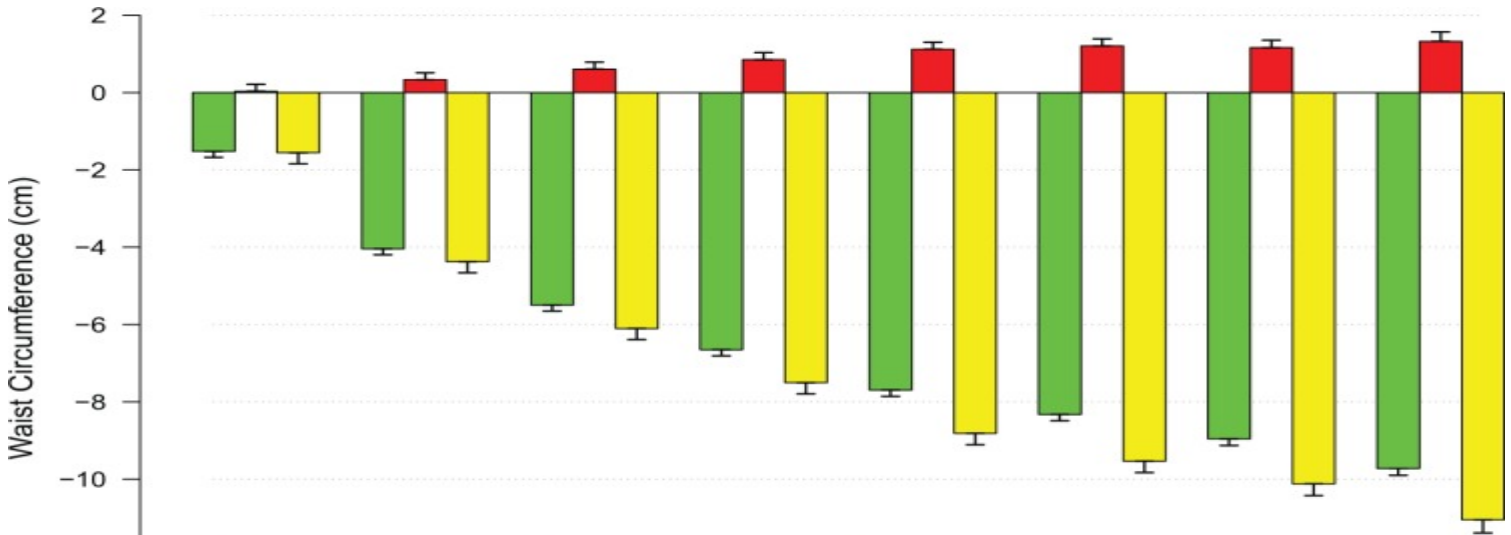

	1 Year	2 Years	3 Years	4 Years	5 Years	6 Years	7 Years	8 Years
Treated	360	356	341	310	255	224	199	160
Control	295	295	295	285	280	246	164	55

Traish AM, et al. J Cardiovasc Pharmacol Ther. 2017;22(5):414-433

Cardiovascular risk associated with testosterone-boosting medications: a systematic review and meta-analysis

Study Design	• Systematic review and meta-analysis of all placebo-controlled randomized clinical trials (RCTs) on the effect of TS on CV-related problems
Materials	• Out of 2747 retrieved articles, 75 were analyzed, including 3016 and 2448 patients in TS and placebo groups, respectively, and a mean duration of 34 weeks
Results	• TS is not related to any increase in CV risk, even when composite or single adverse events were considered • In RCTs performed in subjects with metabolic derangements a protective effect of TS on CV risk was observed.
Conclusion	• Data does not support a causal role between TS and adverse CV events • Results support treatment of hypogonadal men as a valuable strategy in improving a patient's metabolic profile, reducing body fat and increasing lean muscle mass, which would ultimately reduce the risk of heart disease

Corona G, et al. Expert Opin Drug Saf. 2014;13(10):1327-51

Risk of Myocardial Infarction in Older Men Receiving Testosterone Therapy

Study Design	• To examine the risk of myocardial infarction (MI) in a population-based cohort of older men receiving intramuscular testosterone
Materials	• 6355 patients treated with at least 1 injection of testosterone between January 1, 1997, and December 31, 2005 • Matched cohort to 19 065 testosterone nonusers • Patients were followed until December 31, 2005, or until they lost coverage from Medicare, enrolled in a health maintenance organization, experienced a MI, or died.
Results	• Testosterone therapy was not associated with an increased risk of MI (hazard ratio [HR] = 0.84; 95% CI = 0.69–1.02) • For men in the highest quartile of the MI prognostic score, testosterone therapy was associated with a reduced risk of MI (HR = 0.69; 95% CI = 0.53–0.92) • There was no difference in risk for the first (HR = 1.20; 95% CI = 0.88–1.67), second (HR = 0.94; 95% CI = 0.69–1.30), and third quartiles (HR = 0.78; 95% CI = 0.59–1.01)

Baillargeon J, et al. Ann Pharmacother. 2014;48(9):1138-1144

Risk of Myocardial Infarction in Older Men Receiving Testosterone Therapy

Conclusion	• Older men who were treated with intramuscular testosterone did not appear to have an increased risk of MI. For men with high MI risk, testosterone use was modestly protective against MI
Limitations	• Information on outcomes and risk factors came from diagnosis codes (?accuracy) • Medicare claims during the study period provided no data on other formulations • No assessment of co-morbid states or other medications (i.e. anti-lipids) • No baseline information • Retrospective study with possible selection bias

Baillargeon J, et al. Ann Pharmacother. 2014;48(9):1138-1144

Effects of Testosterone Administration for 3 Years on Subclinical Atherosclerosis Progression in Older Men With Low or Low-Normal Testosterone Levels: A Randomized Clinical Trial

Study Design	• To determine the effect of testosterone administration on subclinical atherosclerosis progression in older men with low or low-normal testosterone levels • Placebo-controlled, double-blind, parallel-group randomized trial involving
Materials	• 308 men 60 years or older with low or low-normal testosterone levels (100-400 ng/dL; free testosterone <50 pg/mL) • 156 randomized to receive 7.5 g of 1% testosterone • 152 randomized to receive placebo gel packets daily for 3 years • Dose adjusted to achieve levels between 500 and 900 ng/dL.
Results	• Rate of change in intima-media thickness was 0.010 mm/year in the placebo group and 0.012 mm/year in the testosterone group (P = .89) • Rate of change in the coronary artery calcium score was 41.4 Agatston units/year in the placebo group and 31.4 Agatston units/year in the testosterone group (P = .54)

Basaria S, et al. JAMA 2015:314(6):570-81.

Effects of Testosterone Administration for 3 Years on Subclinical Atherosclerosis Progression in Older Men With Low or Low-Normal Testosterone Levels: A Randomized Clinical Trial

Conclusion	• Testosterone administration for 3 years vs placebo did not result in a significant difference in the rates of change in either common carotid artery intima-media thickness or coronary artery calcium
Limitations	• Sexual desire, erectile function, overall sexual function scores, partner intimacy, and health-related quality of life did not differ significantly between groups • Because this trial was only powered to evaluate atherosclerosis progression, these findings should not be interpreted as establishing cardiovascular safety of testosterone use in older men

Basaria S, et al. JAMA 2015:314(6):570-81.

Testosterone Treatment and Coronary Artery Plaque Volume in Older Men With Low Testosterone.

Study Design	• Double-blinded, placebo-controlled trial at 9 US academic centers testing hypothesis that testosterone treatment of older men slows progression of noncalcified coronary artery plaque volume
Materials	• 170 aged 65 years or older with an average of 2 serum testosterone levels lower than 275 ng/dL • 82 men assigned to placebo • 88 to testosterone gel adjusted to maintain therapeutic level
Results	• Testosterone treatment compared with placebo was associated with a significantly greater increase in noncalcified plaque volume from baseline to 12 months (from median values of 204 mm3 to 232 mm3 vs 317 mm3 to 325 mm3, respectively; estimated difference, 41 mm3; 95% CI, 14 to 67 mm3; P = .003) • Median total plaque volume increased from baseline to 12 months from 272 mm3 to 318 mm3 in the testosterone group vs from 499 mm3 to 541 mm3 in the placebo group (P = .006) • Median coronary artery calcification score changed from 255 to 244 Agatston units in the T group vs 494 to 503 Agatston units in placebo • No major adverse cardiovascular events occurred in either group

Budoff MJ, et al. JAMA 2017;317(7):708-716

Testosterone Treatment and Coronary Artery Plaque Volume in Older Men With Low Testosterone.

Conclusions	• Among older symptomatic hypogonadal men treatment with testosterone gel for 1 year compared with placebo was associated with a significantly greater increase in coronary artery noncalcified plaque volume • Larger studies are needed to understand the clinical implications of this finding
Limitations	• Non-randomization • Different Baseline Groups as see by different baseline plaque volume • Prognostic studies of noncalificied plaque volume non-existent • Questions if increase of fibrous component of plaque increases stability

Budoff MJ, et al. JAMA 2017;317(7):708-716

The Risk of Not Knowing the Absolute Facts

Class Action Suits

Millions of Men at Potential Risk for Fatal Harm Due to Unnecessary 'Low T' Therapy

If you, or a loved one, have been prescribed any of the following low testosterone drugs, you may be entitled to compensation, and should speak to an attorney about your legal rights.

McLaughlin & Lauricella P.C.
Low-T Testosterone Lawsuit Lawyers

Conclusions

- Be vigilant and pick the right patient
- Assess risk of cardiac disease
- Discuss risks and benefits with
  - Patient
  - Primary care
  - Cardiology
  - Urology
- **Document Document Document**